REMARKS

Reconsideration of this application is respectfully requested. Applicants thank the Examiner for the courtesy of the interview on April 19, 2006. As discussed, a Declaration under 37 C.F.R. 1.132 is attached with the current Amendment.

Upon entry of the foregoing amendment, Claims 1-2 and 4-33 will remain pending in the application. Claim 3 has been canceled, Claims 1, 4 and 6 have been amended and Claim 33 has been added. These changes do not introduce new matter, and their entry is respectfully requested.

In the Office Action of February 21, 2006, the Examiner set forth a number of grounds for rejection. These grounds are addressed individually and in detail below.

Specification

All the trademarks recited in the present specification have been amended to be capitalized as suggested by the Examiner.

Claim Rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 6-13 and 28-32 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement for the reasons set forth on pages 4-6 of the Outstanding Office Action. Specifically, the Examiner states that the specification, while being enabling for using a polynucleotide encoding a thrombomodulin protein or its variant, wherein the polynucleotide is operably linked to a regulatory element, does not reasonably provide enablement for using a polynucleotide not operably linked to a regulatory element (see page 6 of the Office Action). In order to expedite prosecution, Applicants have amended independent Claim 1 to recite that "a gutless adenoviral vector which comprises a polynucleotide encoding a thrombomodulin protein or its variant and a regulatory element operably linked to said

polynucleotide sequence . . .". Applicants respectfully submit that the grounds of the rejection have been obviated by the amendment. Withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully submitted.

Claim Rejections under 35 U.S.C. § 112, second paragraph

Claims 3 and 4 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the reasons set forth on page 6 of the outstanding Office Action. Claim 3 has been canceled and Claim 4 has been amended to depend on Claim 1. These grounds of rejection have been obviated and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph is respectfully submitted.

Claim Rejections under 35 U.S.C. § 103

Claims 1, 3, 4, and 8 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,290,949 to French et al. (hereinafter "French") and U.S. Patent No. 5,981,225 to Kochanek et al. (hereinafter "Kochanek") for the reasons set forth on pages 7-9 of the outstanding Office Action. Claims 1 and 5 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over French and Kochanek, and further in view of Salyapongse et al. (hereinafter "Salyapongse") for the reasons set forth on page 9 of the outstanding Office Action. Claims 1, 6, and 7 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over French and Kochanek, and further in view of He et al. (hereinafter "He") for the reasons set forth on page 10 of the outstanding Office Action. Claims 1, 9-13 and 28-32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over French and Kochanek, and further in view of U.S. Patent No. 4,826,811 to Sehgal et al. (hereinafter "Sehgal") and Kibbe et al. (hereinafter "Kibbe") for the reasons set forth on pages 10-12 of the outstanding Office Action. Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Furthermore, when applying 35 U.S.C. § 103, the Examiner is required to adhere to the following tenets of patent law: (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (4) reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.,* 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

In this case, The present independent Claim 1 is directed to **a method for treating a vascular disease** in a mammal, wherein said method comprising the steps of: **infecting a segment of a blood vessel *in vitro*** using a **gutless adenoviral vector** which comprises a polynucleotide encoding a **thrombomodulin protein** or its variant and a regulatory element operably linked to said polynucleotide sequence; **grafting** the virus-treated blood vessel in said mammal, wherein said thrombomodulin protein or its variant is expressed in said virus-treated blood vessel in an amount sufficient to **reduce re-occlusion or intimal hyperplasia in the grafted blood vessel.**

In contrast, French generally describes an *ex vivo* method of gene therapy for treating a vascular disease using the first generation adenoviral vector. As admitted by the Examiner, French does not mention a gutless adenoviral vector. It is clear that the gutless adenovirus vectors of the present Claim 1 are significantly different from the first generation, E1-deleted

adenovirus as described in French. Briefly, the first generation virus vectors contain only a deletion in the E1 gene and have following deficiencies: (1) the virus vectors are highly immunogenic and toxic, and (2) have a limited cloning capacity (typically less than five kb) because of the package limit of the adenovirus.

Kochanek generally describe a gutless adenoviral vector. However, Kochanek neither mentions treating a disease in a mammal using a gutless adenoviral vector nor describes thrombomoduling gene. The Examiner asserts that it would be obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of French taken with Kochanek, and to use a gutless adenoviral vector in French's method. Applicants respectfully disagree because the Examiner is applying an improper "obvious to try" rationale in supporting an obviousness rejection. Further, the Examiner fails to address whether there is reasonable expectation of success, as required by MPEP 2143.02.

It is known in the art that gutless adenoviral vectors are difficult to construct and produce in large quantities. While several methods for producing gutless adenoviral vectors were known to one of ordinary skill in the art at the time of filing, only a limited number of gutless viral vectors were produced and tested in *in vitro* or *in vivo* settings. The major obstacle was that the construction of each gutless viral vector requires extensive experimentation. For example, the shuttle vector needs to contain a stuffer sequence of the proper size so that the total size of the DNA inserted into the gutless viral vector is within the packaging range of the adenovirus. In addition, the level of transgene expression is typically different among viral vectors carrying different transgenes. Therefore, each gutless vector needs to be specifically constructed and optimized for its intended use. At the time of the filing, one of ordinary skill in the art would not successfully construct and produce a gutless adenoviral vector using the teaching of French and Kochanek to practice the present Claim 1 without undue experimentation. As pointed out by the CAFC in *In re O'Farrell*, 853 F.2d

894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988), "[T]he admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. . . In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *Id.* Accordingly, even if one of ordinary skill in the art were to combine French with Kochanek, there would be no reasonable expectation of success, as required by MPEP 2143.02.

The Examiner further recites Salyapongse for its teaching on using an inducible system. He was cited for the description of a simplified system for generating adenoviruses. Sehgal was cited for its teaching on preserving a graft. Kibbe was cited for its teaching on using a 1:1 mixture of Ham's F12 medium and DMEM. Nonetheless, neither of these references mentions the use of gutless adenovirus vectors and cure the deficiency of French and Kochanek.

Applicants would like to call the Examiner's attention to the fact that the present Claim 1 is directed to a medical application of using a **gutless adenoviral vector** which comprises a polynucleotide encoding a **thrombomodulin protein or variant** for treating **a vascular disease**. Neither French, Kochanek, Salyapongse, He, Sehgal, nor Kibbe mentions treating a **vascular disease by infecting a segment of a blood vessel *in vitro*** using a **gutless adenoviral vector** which comprises a polynucleotide encoding a **thrombomodulin protein or variant . . . ; grafting** the virus-treated blood vessel in said mammal . . . in an amount sufficient to **reduce re-occlusion or intimal hyperplasia in the grafted blood vessel.** Consequently, the present invention provides an unexpectedly superior effect for the clinic application for treating thrombic vascular diseases. One skilled in the art would not be able to practice the present Claim 1 based on French, Kochanek Salyapongse, Sehgal, He and

Kibbe without undue experimentation (See attached Declaration of Dr. Sehgal). Thus, it is not obvious to one skilled in the art to derive the present Claim 1 from the prior art of record.

Accordingly, Applicants respectfully submit that French, Kochanek, Salyapongse, Sehgal, and Kibbe, individually or in combination, do not render Claim 1 obvious. Applicants further submit that Claims 4-13 and 28-32 are patentable because they depend from Claim 1 and define additional patentable subject matter. Withdrawal of rejection to Claims 1-13 and 28-32 under 35 U.S.C. § 103(a) is respectfully requested.

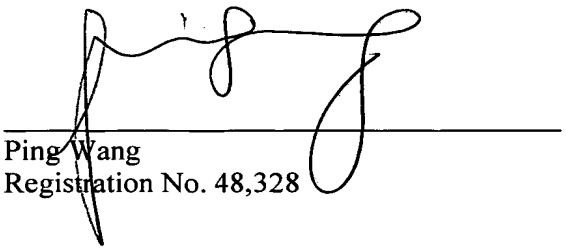
CONCLUSION

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to contact Ping Wang, M.D. (Reg. No. 48,328) at the telephone number listed below.

Respectfully submitted,

DLA PIPER RUDNICK GRAY CARY US LLP



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